DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Dr. Edmund A. Egan, M.D.
President
ONY, Inc.
1576 Sweet Home Road
Amherst, NY 14228

RE: NDA 020521
INFASURF® (calfactant) Intratracheal Suspension
MA #47 and #50

Dear Dr. Egan:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP), Division of Professional Drug Promotion (DPDP) of the U.S. Food and Drug Administration (FDA) has reviewed ONY, Inc.'s webpages, "Home," "Infasurf Product Profile," and "Infasurf Feature and Benefits Video" along with the video titled "Feature and Benefits," which are part of a professional website[1] for INFASURF® (calfactant) Intratracheal Suspension (Infasurf). The webpages and video are false or misleading because they present unsubstantiated superiority claims for Infasurf, omit and minimize important risk information, and present unsubstantiated claims for the drug product. Thus, the webpages and video misbrand Infasurf in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & (n); 321(n). *See* 21 CFR 202.1 (e)(5); (e)(6)(i) & (ii); (e)(7)(viii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Infasurf.[2] According to its FDA-approved product labeling (PI) (in pertinent part):

> Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.
> . . .
> Prophylaxis therapy at birth with Infasurf is indicated for premature infants < 29

[1] Infasurf webpages, "Home" and "Infasurf Product Profile," and "Infasurf Feature and Benefits" including video at http://www.infasurf.com (last accessed July 13, 2012).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.

> weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.
> . . .
> Infasurf therapy is indicated for infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

Infasurf is associated with serious risks. The PI contains Warnings regarding intratracheal use, rapid improvement in oxygenation and lung compliance which necessitate careful monitoring, neonatal intensive care requirements, as well as transient episodes of endotracheal tube reflux, cyanosis, bradycardia, and airway obstruction which require stopping Infasurf administration and taking appropriate measures to alleviate the condition. In addition, the PI contains Precautions regarding an increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) observed in Infasurf–treated infants in the Infasurf-Exosurf Neonatal controlled trials. The Adverse Reactions section of the PI indicates that common complications of prematurity and RDS observed in the four controlled Infasurf clinical trials include apnea, patent ductus arteriosus, intracranial hemorrhage, sepsis, pulmonary air leaks, pulmonary hemorrhage, and necrotizing enterocolitis. The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis, airway obstruction, bradycardia, reflux of surfactant into the endotracheal tube, requirement for manual ventilation, and reintubation.

Unsubstantiated Superiority

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The webpages include claims such as the following:

- “But surfactants differ in other responses that make up the clinical course: Infasurf’s greater potency gives the most rapid and biggest initial improvement in respiratory status when treating patients with RDS.” [*Home*]
- “Infasurf’s high SP-B content prolongs the positive effects, enabling some patients to receive fewer doses.” [*Home*]
- “Infasurf’s high SB-B [sic] content makes it more resistant to inhibition by the serum proteins which form the membranes of Hyaline Membrane Disease.” [*Home*]
- “Infasurf’s formulation produces a dose that is large enough to achieve good distribution. . .in a suspension with the lowest viscosity.” [*Home*]
- “Infasurf is a pure surfactant that contains only active surfactant unlike our competitors, which contain lung tissue contaminants. Infasurf delivers the highest level of Surfactant Protein B (SP-B), the closest to natural lung surfactant.” [*Infasurf Product Profile*]
- “Surfactant Protein-B plays two critical roles: it is the essential activator of the surfactant film and SP-B protects the surfactant film from disruptive inflammatory mediators and this is a concentration dependent response (stoichiometric). The more SP-B you have, the more the film is protected. The less SP-B you have the less the film is protected.” [*Infasurf Product Profile*]

- "Competitive surfactants also create a film but only Infasurf is sufficiently rugged to withstand inhibitory proteins . . . This composition is the reason that Infasurf has optimal immediate and sustained surfactant effects." [*Infasurf Product Profile*]

Similarly, throughout the video comparisons of various properties of the surfactant products are made with regards to concentration, dosing volume, viscosity, SP-B to phospholipid ratio, and length of treatment effect/time to repeat dose. These claims and presentations on the webpages and in the video are misleading because they imply that Infasurf is clinically superior compared to other available surfactants. According to the Clinical Studies section of the PI, the trials used for approval of Infasurf compared it to Exosurf Neonatal® and Survanta®. We note that Exosurf Neonatal® is no longer marketed. The trials which compared Infasurf to Survanta did not demonstrate that Infasurf was clinically superior for either treatment or prophylaxis of RDS. The PI indicates that the efficacy outcomes of incidence of RDS, air leaks, bronchopulmonary dysplasia, and treatment failure, were not significantly different between Infasurf and Survanta. Additionally, there are no references that are specifically cited to support the above claims, and OPDP is not aware of any substantial evidence or substantial clinical experience which demonstrates that Infasurf is clinically superior to other surfactant products. If you have data to support these claims, please submit them to FDA for review.

The video presents the following claims and presentations:

- "As this graph highlights, Infasurf has a more vigorous, more rapid, and more sustained acute effect than Survanta or Curosurf" (voiceover)
- Figure representing "% Inspired Oxygen Concentration" over time for Infasurf and Survanta[3]
- Figure representing "% Inspired Oxygen Concentration" over time for Curosurf and Survanta[4]

These claims and presentations are misleading because they imply that Infasurf is clinically superior to Survanta and Curosurf due to a more rapid and sustained acute effect on respiratory function when this has not been demonstrated by substantial evidence or substantial clinical experience. Neither of the cited references support this implication. Specifically, while the first study, Bloom et al., did evaluate the effects of Infasurf and Survanta on respiratory function, this study measured physiologic data (% inspired oxygen concentration) that has not been demonstrated to correlate with any clinically relevant variables. Therefore, the Bloom et al. study does not constitute substantial evidence to support that Infasurf is clinically superior to Survanta as implied by the above-mentioned claims and presentations. The second study, Ramanathan et al., also evaluated respiratory function, but it was designed to compare Curosurf to Survanta and did not include Infasurf as a comparator in the study. Because Infasurf was not included in this study, no conclusions can be drawn regarding the efficacy of Infasurf on the basis of this study and therefore, the study does not constitute substantial evidence to support claims of superiority

[3] Bloom BT, Kattwinkel J, Hall RT, et al. Comparison of Infasurf (calf lung surfactant extract) to Survanta (Beractant) in the treatment and prevention of RDS. *Pediatrics*. 1997;100:31-38.
[4] Ramanathan R, Rasmussen MR, Gerstmann DR, et al. A randomized, multicenter masked comparison trial of poractant alpha (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. *Am J Perinatol.* 2004;21:109-119.

for Infasurf.

The numerous misleading unsubstantiated superiority claims regarding Infasurf presented throughout the webpages are extremely concerning given the vulnerable patient population.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The webpages and video present the following claim, "During dosing with INFASURF, the most common adverse reactions reported in clinical trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), and ETT reflux (21%)." This claim is misleading because it completely omits other significant common adverse reactions associated with Infasurf dosing. Specifically, the PI states that the most common adverse reactions also include "requirement for manual ventilation (16%), and reintubation (3%)." The omission of this important risk information misleadingly suggests that Infasurf is safer than has been demonstrated by substantial evidence or substantial clinical experience. We acknowledge that the webpages include a link to the PI; however, this does not mitigate the misleading omission of important risk information from the webpages and video.

Furthermore, promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information related to the effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. The video, which is three minutes and 32 seconds in duration, presents many claims regarding the efficacy of Infasurf, but minimizes the risks of Infasurf by failing to disclose **any** of the risks associated with the use of Infasurf during the audio presentation. Additionally, the presentation of the risks associated with Infasurf is relegated to the last seven seconds of the video in read-only text format. This presentation is further exacerbated by the fact that the font presented in the video is blurry and difficult to read. We acknowledge that the "Feature & Benefits Video" webpage where the video is located includes risk information for Infasurf; however, this limited risk presentation is relegated to the bottom portion of the webpage below the video, in read-only text format, where it is unlikely to draw the viewer's attention. Therefore, this overall presentation misleadingly minimizes the risks associated with Infasurf because it fails to convey this important risk information with a prominence and readability reasonably comparable to the claims of effectiveness.

The "Home" webpage presents the following claim (emphasis added):

- "Infasurf's formulation produces a dose that is large enough to achieve good distribution, small enough to be **well tolerated** and in a suspension with the lowest viscosity."

Similarly, the video presents the following claim (emphasis added):

- "Infasurf's concentration produces a dosing volume that is large enough to achieve

good distribution, small enough to be **well-tolerated**, and in a suspension with a lower viscosity than Survanta or Curosurf."

These claims are misleading because they minimize the serious risks associated with the use of Infasurf. The Warnings section of the PI indicates that during Infasurf administration reflux into the endotracheal tube, cyanosis, bradycardia, and airway obstruction have occurred. Furthermore, according to the Precautions section of the PI, "An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials." In addition, according to the Adverse Reactions section of the PI, the most common adverse events associated with Infasurf dosing procedures in the controlled trials included cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubaton (3%). Claims that characterize Infasurf as "well-tolerated" are particularly concerning in light of these serious risks which are associated with the use of this product.

The overall effect of these presentations undermines the communication of important risk information for Infasurf, thereby misleadingly suggesting that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Claims

The "Home" webpage presents the claims, "Lower mortality is the most important benefit of surfactant therapy. **All surfactants** are **equivalent** for that benefit" (emphasis added). These claims are misleading because they imply that Infasurf has been demonstrated to be "equivalent" to all other surfactants in terms of the clinical benefit of lowered mortality in patients with RDS. However, there is no reference cited to support these claims. OPDP is not aware of substantial evidence or substantial clinical experience to support this implication. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the webages and video misbrand Infasurf in violation of the FD&C Act, 21 U.S.C. 352(a) & (n); 321(n). *See* 21 CFR 202.1 (e)(5); (e)(6)(i) & (ii); (e)(7)(viii).

OPDP requests that ONY, Inc. immediately cease the dissemination of violative promotional materials for Infasurf such as those described above. Please submit a written response to this letter on or before November 15, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Infasurf that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and

elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #47 and 50 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Infasurf comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Roberta Szydlo, R.Ph.
Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
Team Leader
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/s/

ROBERTA T SZYDLO
10/31/2012

LISA M HUBBARD
10/31/2012